Catastrophic antiphospholipid syndrome: management challenges and lessons learnt in the third world set-up: Case report

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Abstract

Background: Antiphospholipid Syndrome (APS) is a disorder that manifests clinically as recurrent venous or arterial thrombosis and/or foetal loss. Catastrophic Antiphospholipid Syndrome (CAPS) is a very severe variant of the classic APS. It is characterized by clinical evidence of multiple organ involvement developing over a very short period of time, histopathological evidence of multiple small vessel occlusions and laboratory confirmation of the presence of antiphospholipid antibodies, usually in high titre. Although patients with catastrophic APS represent less than 1% of all patients with APS, this is usually a life-threatening condition. The majority of patients with catastrophic APS end up in intensive care units with multi-organ failure. Making the diagnosis is challenging and can be missed. Unless the condition is considered in the differential diagnosis by attending physicians, it may be completely missed, resulting in a disastrous outcome. Catastrophic APS develops rapidly and can result in death of up to 30-50% of cases.

Case presentation: A nineteen year old nulliparous lady diagnosed with Systemic Lupus Erythematosus (SLE) four months prior to admission with no prior history of thrombo-embolic events presented at the accident and emergency department with one day history of fevers and convulsions. This was associated with history of progressively worsening memory loss and confusion associated with incoordination of hands. She also reported to have had a productive cough of 3 months which was episodic. The patient was admitted and developed multiple organ failure from lungs, heart and the kidney during treatment in hospital attributed to this disease. She succumbed during treatment.

Key words: Antiphospholipid syndrome, Catastrophic antiphospholipid syndrome, Arterial and venous thrombosis, Clinical features, Diagnosis, management

Introduction

Antiphospholipid Syndrome (APS) is a multisystem autoimmune condition characterized by vascular thromboses with or without pregnancy loss associated with persistently positive antiphospholipid antibodies (aPL). The "catastrophic" variant of the antiphospholipid syndrome was first described by Ronald Asherson in 1992[1]. He described it as a condition that develops over a short period characterized by multiple vascular occlusive events usually affecting small vessels. Catastrophic APS (CAPS) is the most severe form of APS with multiple organ involvement developing over a short period of time, usually associated with microthrombosis. Although less than 1% of patients with APS develop this complication[2], its potentially lethal outcome underlines its importance in clinical medicine today. Most of the patients with catastrophic APS will end up in the intensive care units with multi-organ failure. If this condition is not considered in the differential diagnosis by attending physicians, it may be completely missed, resulting in a disastrous outcome[3]. 'Definite' and 'probable' CAPS have been defined based on the preliminary classification criteria; however, in a real-world setting, aPL-positive patients with multiple organ thromboses and/or thrombotic microangiopathies exist who do not fulfil these criteria. Previous APS diagnosis and/or persistent clinically significant aPL positivity is of great importance for the CAPS diagnosis; however, almost half of the patients who develop CAPS do not have a history of aPL positivity. The classification criteria for catastrophic antiphospholipid syndrome are summarized in Table 1. In this article we describe a patient with probable catastrophic APS and the challenges in making the diagnosis and managing this disease.

Case report

A 19 year old nulliparous lady with SLE with no history of thrombo-embolic events and was taking azathioprine, prednisolone, hydroxychloroquine, meloxicam, pantoprazole. She presented at the accident and emergency department with one day history of fevers and convulsions. The patient had been well until two months prior to admission when she started having bouts of recurrent fevers. She was put on various antibiotics during this period with some improvement. Two weeks prior to admission there was a reported history of progressively worsening memory loss and confusion associated with incoordination of hands. During this period she had complained of headaches which the informant wasn't able to describe well in detail. On the day of admission she was reported to have had four convulsions. They were described as generalised tonic clonic seizures lasting about one minute. She had a productive cough of 3 months duration which was episodic. The cough was occasionally blood stained and had worsened over the week prior to admission. There was no positive history of contact with a pulmonary tuberculosis patient. There were no night sweats but had some weight loss which the informant wasn't able to quantify.

Examination on admission revealed mild confusion, intention tremors with a Glasgow coma scale of 13/15 and oral thrush. She was noted to be disoriented in time, place and person. The neck was soft kerning's negative with no noted focal neurological deficit. Respiratory examination showed mild respiratory distress with bilateral basal crepitations. Her cardiovascular exam showed tachycardia with normal heart sounds. The abdominal exam only revealed suprapubic tenderness. The diagnosis at this time was active lupus with sepsis.

The laboratory investigations are summarized in Table 2. Other tests done included lactate dehydrogenase at 974 IU/L (High), Creatinine Phosphokinase (CPK) at 113mcg/L (Normal), Creatinine Kinase (CKMB) at 33.2ng/ml (Normal), Magnesium at 0.92mg/dl (normal), Calcium at 1.28 mg/dl (low). C-reactive protein was elevated at 14 mg/l, urinalysis had protein 2++, specific gravity 1030, PH at 5, granular cast and Procalcitonin was 0.1 ng/l. A head Computed Tomography scan was reported as normal. A lumber puncture yielded clear Cerebrospinal Fluid (CSF), microscopy normal, biochemistry had proteins increased at 60.6g/dl with normal glucose at 4.3mmol/l. The CSF also tested negative for cryptococci antigen and tuberculosis via PCR. ECG revealed a sinus tachycardia. She had elevated troponins at 0.3 ng/ml and elevated D-Dimers at >5000ug/l and a normal International Normalised Ratio (INR). Her chest X-ray showed reticulonodular infiltrates bilaterally.

The patient was admitted to high dependence unit. She was reviewed by the neurology team who queried neuro-lupus and ordered for brain magnetic resonance imaging. The chest team started her on anti-tuberculosis drugs based on fever, productive cough and the fact she had been on antibiotics with no improvement and requested for a high resolution chest Computed Tomography scan. The psychiatric team made a diagnosis of acute organic confusional state with mood disorders and started the patient on olanzapine. The patient's general condition improved and she was transferred to the general wards. Four days post admission patient decompensated and was admitted to intensive care unit with the diagnosis of a possible catastrophic antiphospholipid syndrome with pulmonary embolism and acute kidney injury.

The patient was started on soluble insulin, intravenous fluids, clexane and pulsed with methylprednisone. She was started on inotropic support with norepinephrine. The 2D Echocardiograph revealed global hypokinesia, poor Left ventricular function, no tricuspid regurgitation with pulmonary arterial pressure of 35mmhg, dilated left atrium, mitral regurgitation and ejection fraction of 30%. The renal team recommended continuous renal replacement therapy. Patient still noted to have fevers and pulmonary crepitations. lab results showed C-reactive protein at 168mg/l; culture of stool, blood and urine had no growth; Procalcitonin 0.1ng/ml; activated partial thromboplastin time test 94.5 sec, control 25 sec; Prothrombin time test 24 sec, control 12.5 sec; PCR for tuberculosis was negative; Lupus anticoagulant was positive while anticardiolipin was negative. Patient eventually succumbed while undergoing treatment.

Table 1: Preliminary classification criteria for catastrophic antiphospholipid syndrome

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small-vessel occlusion*
4. Laboratory confirmation of the presence of antiphospholipid antibodies†

Definite catastrophic antiphospholipid syndrome

- All four criteria present

Probable catastrophic antiphospholipid syndrome

- All four criteria, except only two organs, systems, and/or tissues involved
- All four criteria, except for the absence of laboratory confirmation of antiphospholipid antibodies
- Criteria 1, 2, and 4

*Vasculitis may coexist, but significant thrombosis must be present as well
†"Positive aPL" twice 12 weeks apart[25]

Table 2: Laboratory results

Day admission	Day 1 ICU	Day 3 ward	Day4 ward	Day 1 ICU	Day 2 ICU
Na	133		134	135	134
K	4.5		4.4	4.3	4.2
Urea	4.3		11.7	5.1	5.4
Creatine	58		280	129	94
Total bilirubin	8		18.8	34.9	35.9
Direct bilirubin	3.5		13.5	26.5	24.7
ALT	59	25	18	30	210
AST	164	79	94	590	5,554
GGT	188	239	266	246	191
Total protein	75	60	60	63	55
Albumin	31	39	22	22	23

Day 1 ICU	Day 2 ICU	Day 3 wards	Day 1 ICU	Day 2 ICU
WBC 4.08	8.25 N-60.3	16.7 N-81.8	11.6 N-81.7	5.05 N-90.8
HB 12.3	12.8	12.8	10.6	7.11
MCV 81.7	82.3	80.7	80.9	78.7
PLT 350	293	274	376	204

Na= Sodium; K=Potassium; Alt=Alanine Transaminase; Ast= Aspartate Transaminase; GGT=Gamma Glutamyl Transferase; WBC=White Blood Cells; N=Neutrophils; HB=Haemoglobin; MCV= Mean Corpuscular Volume; Plt= Platelets

Table 3: How to distinguish the various differential diagnosis of catastrophic antiphospholipid syndrome

	Fibrinogen	Haemolytic anaemia	Schistocytes	Thrombocytopenia	APL
CAPS	Normal	Present/Absent	Present	Present/Absent	Present
Sepsis	Normal/Low	Present	Present/Absent	Present/Absent	Present/Absent
TTP-HUS	Normal	Present	Present	Present	Absent
DIC	Low	Present/Absent	Present/Absent	Present	Absent

APL=Antiphospholipid Syndrome; CAPS=Catastrophic Antiphospholipid Syndrome; DIC=Disseminated Intravascular Coagulation; TTP-HUS=Thrombotic Thrombocytopenic Purpura – Haemolytic-Uraemic Syndrome

Discussion

Though APS is one of the most common and fatal thrombocytophilias, it is unfortunately not often looked for and diagnosed. 2–5% of the general population will have detectable anticardiolipin antibodies of which 30–50% of those persons may have symptoms of APS. Patients with recurring thrombosis, especially in an atypical localization or an atypical aetiology and recurrent fetal wastage, APS should be considered[6]. Our patient did not have a history of recurrent thrombosis and fetal wastage. We thought of it only when she decompensated a second time and now the diagnosis of CAPS was made. She had multiple organ dysfunction within a short duration of time in the background of SLE. CAPS is the most severe form of APS with multiple organ involvement developing over a short period of time, usually associated with microthrombosis. The classification criteria for catastrophic antiphospholipid syndrome are summarized in Table 3. Although less than 1% of patients with APS develop this complication[2], its potentially lethal outcome underlines its importance in clinical medicine today. The diagnosis of CAPS can be challenging because of the acute onset of thrombosis

at multiple levels with simultaneous dysfunction of different organs. The survival of the patients very much depends on an early diagnosis and treatment. Attempts at documenting the world wide epidemiology has been a challenge due to difficulties in making the diagnosis. In the local set up and Africa as a whole there has been no case report of this rare but fatal disease. This can be attributed to low level of suspicion and limitations from finance and infrastructure support of laboratory and radiological services. In a review by Cervera *et al*[4] of 280 patients with CAPS from the website-based international CAPS registry shows that 72% were female, with a mean age of 37 years (range 11–60 years). Approximately 46% had primary APS and 40% SLE[4]. Our patient was female, younger than the mean age at nineteen years and was known to have SLE.

The aetiology and pathogenesis of CAPS is an enigma and remains incompletely understood. Several mechanisms have been proposed such as molecular mimicry, infections and activation of endothelium in the microvasculature and microvascular occlusions[7]. It's suggested that the vascular occlusions are responsible for fueling the ongoing thrombosis[8]. It's postulated that clots continue to produce thrombin, an increase in plasminogen activator inhibitor type-1 impairs fibrinolysis. This is compounded by the consumption of the natural anticoagulant proteins such as protein C and antithrombin. These multiple small vessel occlusions cause extensive tissue necrosis which results in a Systemic Inflammatory Response Syndrome (SIRS), with excessive cytokine release from affected and necrotic tissues[9]. Proinflammatory cytokines together with products of the activated complement system (e.g., C3b, iC3b and C5a) and APL antibodies themselves have each been demonstrated to activate endothelial cells thus providing a stimulatory signal and up-regulate adhesion molecules and tissue factor. These molecules are thought to act on leukocytes and platelets to increase their adhesion to vascular endothelium. This promotes microthrombosis and the local release of toxic mediators, including proteases and oxygen-derived free radicals. In the presence of APL antibodies these cells interact leading to the diffuse microvasculopathy that characterizes CAPS and leads to multi-organ failure[7-10].

Clinical manifestations of CAPS

The clinical manifestations of CAPS depend on the organs that are affected, by the thrombotic events and the extent of the thrombosis, together with manifestations of the SIRS. Unlike classic APS where single venous or arterial medium to large blood vessel occlusions are common it is rare in patients with catastrophic APS. Multiple organ dysfunction and failure, as a consequence of thrombotic microangiopathy, are responsible for the majority of the clinical features. The most common known trigger for CAPS is infection. Other less common causes are anticoagulation withdrawal or low INR, medications (e.g., oral contraceptive), obstetric complications, neoplasia, systemic lupus erythematosus flares, trauma and surgery. In almost half of the cases, no obvious precipitating factors have been identified and CAPS can often occur in patients without any previous thrombotic history[1]. Our patient had no thrombotic history. We suspected a combination of a pulmonary infection and an SLE flare as the triggers of this CAPS episode.

She had presented with respiratory and neurological symptoms on admission. These are the two most common presentations of CAPS. In a review by Cervera *et al*[4] of 280 patients with CAPS from the website-based international CAPS registry they reported that the first clinical manifestation at the time of the catastrophic episode was a pulmonary complication in 24% of the cases, a neurologic feature in 18% and a renal feature in 18%. In our case the initial manifestation was a neurological manifestation as seizures and memory loss. Although the initial presentation of CAPS may involve a single organ, in a very short period of time, typically days to weeks, patients develop clinical evidence of multiple organ thrombosis and dysfunction leading to organ failure that requires Intensive Care Unit (ICU) admission. The patient was admitted in ICU with multi-organ failure involving the neurological, respiratory, renal, haematological and hepatic systems. This is in keeping with data by Cervera *et al*[4]. In the same review on the cohort of CAPS patients[4] during the catastrophic episode, intra-abdominal involvement was identified in the majority of patients, mainly consisting of renal (71%) followed by hepatic (33%), gastrointestinal (25%), splenic (19%), adrenal (13%) and pancreatic (8%) manifestations. Respiratory complications (64%) were common mainly acute respiratory distress syndrome and pulmonary embolism, but occasionally intra-alveolar haemorrhage. Cardiac manifestations (51%), were mainly cardiac failure and myocardial infarction or valve lesions. Cerebrovascular complications were present in 62%, mainly consisting of encephalopathy and cerebrovascular accidents with a smaller number of seizures, headache or silent brain infarcts. Skin manifestations represented 50% with features including leg ulcers, purpura, splinter haemorrhages livedo reticularis, necrotic lesions, digital gangrene, and multiple ecchymosis. Less numbers of deep venous thrombosis (23%) and peripheral arterial occlusive disease (11%) were detected. Rarer manifestations reported included retinal involvement (7%), mononeuritis multiplex (5%) and bone marrow necrosis (4%) [4].

What are the diagnostic challenges in CAPS?

Making the diagnosis of CAPS can be an enigma. There are many conditions that mimic CAPS. Examples include sepsis, Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic Uremic Syndrome (HUS). Sepsis was high on our list of differentials because of fever, multiple organ involvement with suggestive laboratory findings in a short duration of time. We suspected the foci of infection to have originated from the lungs. When sepsis is associated with DIC potential complications include bleeding, thrombocytopenia, and microthrombosis; all are also common in CAPS patients. Thus, both the pathophysiology and clinical manifestations of CAPS resemble sepsis with the ultimate development of multiple organ dysfunction syndrome. DIC can also mimic CAPS. The two are similar as they are multi-systemic involving renal, liver, lung and central nervous

system involvement. CAPS differs from it as it has less widespread haemorrhage. Our patient had multi-organ involvement but no widespread haemorrhage.

TTP, HUS and haemolysis, elevated liver enzymes and Low Platelets (HELLP) syndrome which have to be considered were also considered. These was because of deranged liver function tests but were dropped due to lack of significant haemorrhage, haemolysis and low platelets (Table 3). Some of these conditions at times overlap with CAPS as part of a continuum of thrombotic microangiopathy conditions and can present a diagnostic challenge in differentiating them.

To make the diagnosis of CAPS, there should be clinical evidence of multiple organ involvement developed over a short period of time, histopathologic evidence of multiple small vessel occlusions and laboratory confirmation of the presence of aPL, usually in high titer (Table 1). The presence of APL, namely anticardiolipin, antib2-glycoprotein I and lupus anticoagulant is mandatory for the diagnosis The positivity of aPL should be confirmed also later, when the acute clinical situation is over. Our patient tested positive for lupus anticoagulant but negative for anticardiolipin. There are controversies about the antibodies used to diagnose APL. A false positive APL test can be associated with infections (usually low-titer APL ELISA) [11-13]. Patients on anticoagulation may also have positive LA. In APS or CAPS patients, rarely APL antibodies become transiently negative at the time of thrombosis possibly theories including its consumption during the disease process[14-15]. From her short history, multiple organ involvement and lab tests we think she may have had probable CAPS though a histopathological diagnosis may have been useful in clinching the final diagnosis.

Prognosis and treatment

Mortality from this condition is usually high due to diagnostic challenges and lack of sufficient large population based trials on treatment. Our patient succumbed very early during treatment despite involvement of multi-disciplines and the various therapeutics offered to her. Catastrophic APS develops rapidly and leads to death in 30% of cases. They need adequate management in ICU that should include haemodialysis, mechanical ventilation or cardiovascular support for shock. Other factors like aggressive treatment of infection, debridement or amputation of necrotic tissues/organs, careful management of intravascular instrumentation, especially arterial which can lead to new clots, are extremely important and can substantially improve the rate of survival.

The optimal treatment regimen for CAPS is unknown. Current treatment guidelines suggest that early diagnosis and aggressive therapies are necessary to avoid the potentially fatal outcome. The combination of high doses of intravenous (iv) heparin, iv. steroids, iv immunoglobulins and/or repeated plasma exchanges are the basic treatment of choice for all patients with this severe condition (Evidence Level II)[16] .

In the absence of a clinical randomized control trial, anticoagulation (AC) together with corticosteroids (CS) is the most commonly used regimen (19.8%). We were able to put the patient on anticoagulation and corticosteroids which is readily available in our local health set-up. This is followed by anticoagulation with corticosteroids and/or IV immunoglobulins (IVIG) (17.4%). The highest recovery rate is achieved by the combination of AC with CS with Plasma Exchange (PE) (77.8%), followed by anticoagulation with corticosteroids with plasma exchange and/or IVIG (69%)[16]. IV immunoglobulins and plasma exchange are not readily available due to financial implications and their availability locally. Maybe this may have produced better results in our patients. Anticoagulation is usually given in the form of heparin, which is the mainstay of treatment in patients with catastrophic APS[17]. Corticosteroids act by inhibiting nuclear factor-κB, which is an important mediator in both systemic inflammatory response syndrome and APL-mediated thrombosis[18]. However analysis of the CAPS Registry shows that corticosteroids alone does not improve outcome. Plasma exchange clearly improves patient survival by removes APL (most likely transiently), as well as cytokines, tumor necrosis factor-alpha, and complement products[19-20].

IVIG has multiple therapeutic points of actions and has been shown to improve the outcome according to the CAPS Registry[21]. There has been promising results on treatment with rituximab, an anti-CD20 monoclonal antibody is effective in catastrophic APS, as evidenced in two patients in a case series that treated with rituximab during the event[22]. Although more data are necessary to support the use of this drug in the setting of CAPS, current experience seems quite promising, especially in patients with severe thrombocytopenia.

Comparing the data on demographic, clinical and immunologic characteristics of patients who survived to those who died several prognostic factors have been identified. They include older age, pulmonary and renal involvement, the presence of SLE and high titre of antinuclear antibodies (ANA) were associated with a higher mortality rate[23]. Our patient had three poor prognostic factors which included the presence of SLE, pulmonary and renal involvement.

There have been case reports of CAPS relapse. Precipitating factors in these patients were infection, sub-therapeutic anticoagulation level and anticoagulation withdrawal. The presenting symptoms were very similar to the first CAPS episode (renal failure followed by cerebral, cardiac and pulmonary involvement) [24].

Conclusions

APS is a systemic autoimmune disease with both thrombotic and non-thrombotic manifestations. CAPS is the most severe form of APS with multiple organ thromboses, usually accompanied by microthrombosis and haematologic manifestations. Although less than 1% of patients with APS will develop this complication, its potentially lethal outcome underlines its significance in clinical medicine today. The clinical manifestations of CAPS may evolve gradually, commonly overlapping with other thrombotic microangiopathies, requiring a high index of clinical suspicion. The majority of patients with catastrophic APS will end up in intensive care units with multi-organ failure and, unless the condition

is considered in the differential diagnosis by attending physicians. This may be completely missed, resulting in a disastrous outcome.

Third world countries have few case reports due to problems from infrastructure of laboratory to radiology services. This means that diagnosis will have to be on level of suspicion. Patients presenting with multi-organ involvement background of lupus or unexplained atypical or recurrent thromboses should be investigated for CAPS. A prompt diagnosis will enable physicians to take measures to prevent death from this syndrome. An aggressive treatment with steroids, anticoagulation and IVIG in an ICU setting, will help prevent the progression of organ failure or the development of septic shock in the infected patients.

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